Chapter

Primary Central Nervous System Neuroblastoma: An Enigmatic Entity

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Abstract

Neuroblastoma is one of the most common solid tumour in the paediatric age group. Central nervous system (CNS) involvement in neuroblastoma is commonly due to metastasis from the extracranial primary. Primary CNS Neuroblastoma (PCNS-NB) is a rare entity and highlights errors in development of neural crest cells and CNS. A lot has been published since the first description of PCNS-NB four decades ago. Over the years, neuroscientists, geneticists, and clinicians have improved the understanding of PCNS-NB. PCNS-NB is an enigmatic entity with variable presentation, epidemiology, clinical features and outcomes. Recent update in knowledge is seen in 2016 WHO classification of CNS tumours with reclassification of CNS neuroblastoma. It further subclassified different histological variants of PCNS-NB and its molecular correlates. Most common histological subtype of PCNS-NB is neuroblastoma followed by ganglioneuroblastoma. Studies support the view that younger age group, less number of lesions, ganglioneuroblastoma histology subtype and surgical management are good prognostic indicators. This chapter provides an updated overview of epidemiology, clinical features, histological and molecular diagnosis, and outcomes of PCNS-NB in addition to the role of adjuvant therapy.

Keywords: Primary central nervous system neuroblastoma, Ganglioneuroblastoma, CNS PNET, CNS Neuroblastoma with FOX-R2, CNS embryonal tumours

1. Introduction

1.1 Background

Neuroblastoma is one of the most common solid extracranial tumour in the paediatric age group. Key characteristics of neuroblastoma include onset at an early age, aggressive behaviour, tendency to metastasize, regress spontaneously in infancy, and variable presentation [1, 2]. Neuroblastoma is associated with grim prognosis with 60% of patients at presentation having only 5–15% chance of long term survival [3]. Most of the cases of central nervous system neuroblastoma are due to metastasis from the extracranial site. Primary central nervous system neuroblastoma (PCNS-NB) is uncommon as metastatic intracranial neuroblastoma (MIC-NB). It is essentialto understand that the manifestation of neuroblastoma varies with the site of origin [4, 5]. Therefore, a PCNS-NB has different epidemiology, clinical features, and outcomes compared to the MIC-NB. There is emerging evidence on various molecular and genetic profiling of neuroblastoma which dominates the clinical

picture. At the end of this chapter, the readers will acquire updated information on the PCNS-NB, various modes of presentation, and treatment outcomes in light of current evidence. Recent research areas, molecular and genetic findings, and areas with gaps of knowledge are also highlights of this chapter.

1.2 History

Horten, and Rubinstein provided the earliest large scale description of 35 cases of PCNS-NB in 1976 [6]. Their description includes the gross description of the tumour, clinical features and management, but lacks the description of the evolution of these tumours. They described three variants of PCNS-NB based on connective tissue stroma and cells with ganglionic differentiation. The classic variant is similar to the peripheral neuroblastoma with relatively high proportions of cells with ganglionic differentiation and high frequency of Homer Wright rosettes. A desmoplastic variant consists of tumours composed of intense connective tissue stroma. A transitional variant consists of tumours with both classical and desmoplastic features [6]. They found 40% to have metastasis along the craniospinal axis at autopsy and reported PCNS-NB to be similar to cerebellar medulloblastoma [6]. Overall three years survival is reported to be 60% and five years survival at 30% [7]. Most of these studies have probably clubbed other tumour types (Medulloblastoma, undifferentiated ependymoma, and sarcoma) in the expectedstandard category of CNS neuroblastoma; hence, they do not provide a precise analysis of this rare entity. Further, most studies on PCNS-NB have variable reporting on the treatment modalities, surgical options, extent of resection, adjuvant chemoradiation and long term outcomes. Therefore PCNS-NB is still one of the least understood neoplasms of the CNS.

1.3 Definition

In 2016 WHO classification of CNS tumours, CNS neuroblastoma is classified under neuronal and paraneuronal tumours with ICD 0 code of 9500/3 [8]. The first four digits of the ICD 0 code indicates the specific histologic term and the fifth digit after/indicates the nature of the tumour with 3 indicating malignant behaviour. Primary central nervous system neuroblastoma (PCNS-NB) is defined as an embryonal tumour with poorly differentiated neuroepithelial cells, groups of neurolytic cells and variable neuropil rich stroma [8]. These tumours carrier grave prognosis and usually portrays aggressive behaviour [4]. Ganglioneuroblastoma is a subtype of neuroblastoma and defined by the International Neuroblastoma Pathology Classification framework based on the Shimada system [9, 10].

1.4 Epidemiology

Neuroblastoma is primarily a neoplastic disease of the peripheral nervous system. Oncologists often describe neuroblastoma as enigmatic heterogenous neoplasia due to its unique features and biological properties of spontaneous regression, aggressive progression and maturation [2, 11, 12]. These variable factors serves as the prognostic factors in the cure and outcome of neuroblastoma [12, 13]. Epidemiology of PCNS-NB differs from the heterogeneous group of neuroblastoma [2]. In general, neuroblastoma is diagnosed most commonly in the first year of life with a median age of diagnosis at 18 months, with 90% of children with neuroblastoma presenting under ten years of age at an estimated prevalence of 25–50 cases per million individuals [14, 15]. However, only cases reports and case series of few patients exist for PCNS-NB. To understand the epidemiology and natural history of PCNS-NB, Lu et al. [16] conducted a population-based study using the SEER

(Surveillance, Epidemiology and End Results) program. The annual incidence of PCNS-NB has shown a downward trend from 1973 to 2013, probably because many of these tumours were earlier labelled as medulloblastoma, undifferentiated ependymoma or sarcoma due to inferior diagnostic methods [16]. As per the SEER program, the annual age-adjusted incidence rate was 0.12 per 1,000,000 persons in 2013 and the incidence decreased with age with peak incidence occurring in infants [16, 17]. No gender or racial variation has been reported for the occurrence of PCNS-NB. In the study by Lu et al. [16], 40.7% of patients belonged to the age group 1–9 years and only 8.2% were of age ≥ 40 years. Mean age of patients in reported literature of PCNS-NB is around five years with slight female preponderance.

1.5 Tumour characteristics

Histologically most common histology of the PCNS-NB is neuroblastoma, followed by ganglioneuroblastoma. In a large population-based study brain (53.6%) was found to be the most common site of PCNS-NB, followed by other nervous system tumours (46.4%). Tumours at sites in the nervous system other than the brain tend to occur in a much younger age group, extensive and more aggressive [16].

1.6 Etiopathogenesis

Neuroblastoma arises from the primitive elements of the neural crest and therefore predominantly affects the neural crest derivatives, i.e. adrenals and sympathetic ganglia. The central nervous system (CNS) can be involved in the form of primary CNS neuroblastoma, CNS metastasis secondary to occult primary, primary intraorbital neuroblastoma from the ciliary ganglion, metastatic neuroblastoma to the orbit, primary intraspinal neuroblastoma originating from dorsal root ganglion, metastatic spinal neuroblastoma and remote paraneoplastic effects such as myoclonic encephalopathy. WHO classification of CNS tumours (2007) enlist CNS-PNET-NOS (not otherwise specified) and four variants of CNS PNET which can be differentiated based on molecular characteristics as CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma and ependymoblastoma [8]. According to the 2016 WHO classification of CNS tumours, CNS neuroblastoma is classified as an embryonal tumour [8]. CNS-PNET was not found to be a separate entity after the DNA methylation profile of most of the PNET tumours. However, when most well-defined CNS tumours with similar DNA methylation profiles were excluded, there were few unknown tumours, one of which is CNS neuroblastoma [18]. This new molecular entity after DNA methylation was designated as "CNS neuroblastoma with *FOX-R2* activation" (CNS NB-*FOXR2*) [18]. Various studies have elucidated the mechanism for development of CNS disease in a patient of neuroblastoma. Odeone-Filho hypothesised that meningeal surface can act as potential direct pathyway for entry of neuroblastoma cells in the CNS, based on a case with CNS neuroblastma in completely controlled systemic disease.

The development of PCNS-NB does not follow two-hit models usually suggested in neuro-oncology. Instead, it results from the persistence of embryonic cell, which should have differentiated or undergone apoptosis during the ordinary course of CNS development. Bcl-2 family of genes regulate apoptosis, and its continued expression appears to play a significant role in the pathogenesis of neuroblastoma and its resistance to chemotherapeutic drugs. Other genetic factors implicated in neuroblastoma development include cytogenetic aberrations in neuro crest development, partial monosomy for the short arm of chromosome 1, and long arms chromosomes 11 and 14. Shimada system of classification of neuroblastoma

Type	Description
I	Neuroblastoma (Schwannoma stroma-poor)
II	Ganglioneuroblastoma, intermixed (Schwannoma stroma-rich)
III	Ganglioneuroma (Schwannoma stroma-dominant)
IV	Ganglioneuroblastoma, nodular (composite schwannoma stroma-rich/stroma-dominant and stroma-poor)
V	NT, unclassifiable

Table 1.
The international neuroblastoma pathology classification of neuroblastoma (Shimada system) [1].

Stage 1	Complete gross excision of localised tumour, with or without positive microscopic margins	Negative ipsilateral non-adherent lymph node(s) (lymph node(s) attached to and removed with the primary tumour may be positive)
Stage 2A	Incomplete gross excision of localised tumour	Negative ipsilateral non-adherent lymph node(s) (lymph node(s) attached to and removed with the primary tumour may be positive)
Stage 2B	Complete or incomplete gross excision of localised tumour	Positive ipsilateral non-adherent lymph node(s); contralateral lymph node(s) negative for tumour
Stage 3	a. Unresectable unilateral tumour infiltrating across the midline OR b. Localised unilateral tumour OR c. Unresectable midline tumour with bilateral extension	a. Positive or negative regional lymph node(s) OR b. Contralateral positive regional lymph node(s) OR c. May be "unresectable" due to positive bilateral lymph node(s)
Stage 4	Any primary tumour with involvement of distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except 4S)	
Stage 4S	Any localised primary tumour with involvement of skin, liver, and/or less than 10% of bone marrow cellularity (ONLY applies to children less than 1 year of age)	

Source: [9].

Table 2.
International neuroblastoma staging system.

and International Neuroblastoma Staging System is illustrated in **Tables 1** and **2**, respectively. There are even reports of neuroblastoma occurring post-radiation in children and adults [19–22].

1.7 Clinical features

Patients usually present with features of intracranial mass lesion and raised intracranial pressure. Secondary neuroblastoma is mainly extra-axial pathology. It presents as a bony lesion involving the calvaria and extradural mass lesion. However, the lesion can produce haemorrhagic deposits in the parenchyma and increase intracranial

pressure and altered neurological status. Presentation with seizures is not very common. Extra-axial deposits of neuroblastoma present with neurological deficits due to compression of eloquent brain parenchyma. These lesions can also have sutural diastasis due to epidural deposits along the sutures and do not indicate raised intracranial pressure. The status of venous sinuses should be evaluated with CT and MR imaging in patients with sutural diastasis as increased intracranial pressure will show compression of venous sinuses, which will be absent in sutural diastasis due to neuroblastoma deposits [23]. PCNS-NB being intra-axial pathology presents headaches, vomiting, ill localised features, localising features based on cerebral location, and raised intracranial pressure and seizures. Many of these patients present with clinical features on intraventricular mass lesions and hydrocephalus. There can be sudden worsening in the neurological status in the event of a haemorrhage within the lesion.

2. Imaging and histopathology

2.1 Imaging

A typical CT picture of PCNS-NB shows a large intra-axial lesion with calcifications, cystic degeneration and areas of haemorrhage [24]. Perilesional oedema may be limited as compared to the size of the lesion [24]. On post-contrast CT images, uniform enhancement is seen in solid masses, and heterogeneous contrast enhancement is seen in lesions with cystic degeneration and extensive calcifications. Additionally, intraventricular lesions can demonstrate subependymal masses and help in differentiating these lesion from other differential diagnoses of intraventricular mass lesions. MR imaging of these tumours shows inhomogenous intensities on both T1 and T2-weighted images [24]. Areas of calcification and flow voids can be challenging to identify in classical MRI and can be seen well in susceptibility-weighted images (SWI). Different duration of haemorrhage within the lesion can be appreciated well on MR images. On gadolinium-enhanced T1-weighted MR imaging, tumour mass shows inhomogeneous contrast enhancement. Contrast MRI further helps in identifying subependymal enhancement, recurrence around previously operated sites and leptomeningeal spread. Imaging also helps to assess ventricular size as these tumours grow towards the ventricles and many patients develop secondary hydrocephalus. As there are no pathognomonic image findings of PCNS-NB, it should be kept in the differential diagnosis of any patients with the clinical possibility of PCNS-NB and intra-axial, intraventricular or periventricular mass lesion [24]. Primary CNS neuroblastoma is usually intra-axial and spread through CSF pathways, whereas secondary neuroblastoma is mainly extra-axial but can have haemorrhagic deposits in the parenchyma and sutural diastasis on CT due to epidural deposits [23].

2.2 Histopathology

Grossly PCNS-NB tumours are massive, discrete, firm, and cystic in appearance. Histopathology of a newly designated group of tumours as CNS neuroblastoma which were earlier designated as CNS neuroblastoma or CNS ganglioneuroblastoma in 2007 WHO classification scheme [8] showed distinct characteristics. CNS NB-FOXR2 showed an embryonal architecture with small cells and areas of differentiation in neuropil, neurocytic cells and ganglion cells with uniform expression of OLIG2 and neuronal antigen synaptophysin (**Figure 1**) [13, 18]. Histologically ganglioneuroblastoma consists of ganglion cells with different degrees of differentiation, Nerve sheath, glial fibres, and malignant neuroblastoma cells [9, 25–27]. Common pathological picture of ganglioneuroblastoma includes

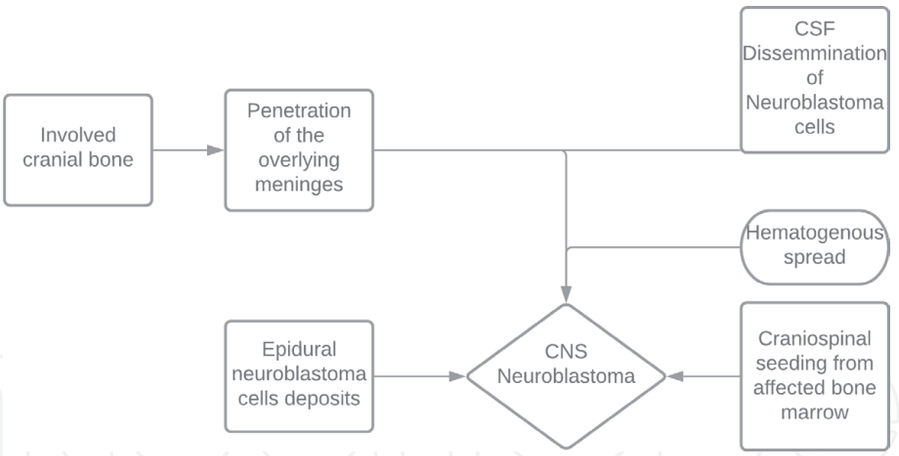

Figure 1.
Various routes for entry of neuroblastoma cells, and its spread to and within CNS.

ganglion cells with a double nucleus, highly infiltrated and proliferated cells with dense chromatin [28, 29]. Further ganglioneuroblastomata have two histological subtypes: undifferentiated type has a small round to oval cells with hyperchromatic nuclei, and poorly differentiated type has a large round to oval spindle-shaped cells with pale staining nuclei [30, 31].

2.3 Discussion

Neuroblastoma is an enigmatic and one of the most common malignant solid tumour of the paediatric age group. Neuroblastoma is a disease with a grim prognosis, and the outcome has not changed significantly in the past two decades. Neuroblastoma teaches us essential aspects of CNS and neural crest development. Primary CNS Neuroblastoma (PCNS-NB) is a rare subtype of neuroblastoma with variable classification. It includes CNS neuroblastoma and ganglioneuroblastoma. In 2016 WHO classification of CNS tumours, PCNS-NB is classified as embryonal tumours. Embryonal tumours with the exception of medulloblastoma has been reclassified based on molecular alterations, for example atypical teratoid rhabdoid tumour (AT/RT) characterised by SMARCB1 or SMARCA4 inactivation, C19MC altered and/or LIN28A expressing embryonal tumour with multi-layered rosettes (ETANTR) and CNS neuroblastoma/Ganglioneuroblastoma without specific histological features or molecular alterations [8]. Based on global transcriptional and methylation profiling four tumour entities have been proposed: CNS neuroblastoma with FOXR2 activation (NB-FOX-R2), High grade neuroepithelial tumour with MN1 alteration (HGNET-MN1), high grade neuroepithelial tumour with BCOR alteration (HGNET-BCOR), and Ewing sarcoma family tumour with CIC alteration (EFT-CIC) [18]. CNS neuroblastoma rarely contains GFAP positive cells which are usually reactive astrocytes and most of the NB-FOX-R2 tumours are neuroblastic differentiation and contains neurocytic cells with poorly differentiated neuropil rich stroma and embryonal architecture [32]. However, there are reports of CNS neuroblastoma with GFAP positive tumour cells demonstrating both neuronal and glial nature, though the clinical significance of such entity is unknown [32]. Since, PCNS-NB is a rare entity and usually present in younger age group, little is known about its treatment protocols, prognostic factors and patient risk stratification. Review of literature suggests that PCNS-NB preferentially occurs in the supratentorial space with involvement of frontal and parietal region [4]. Clinical presentation of PCNS-NB is usually as per the most common site of involvement. Since, most of the PCNS-NB prefers supratentorial location preferably in the frontal and parietal region, patients

usually manifest with focal neurological deficits, bony lesions, irritative symptoms in form of seizures and symptoms of raised intracranial pressure due to mass effect. These effects of raised intracranial pressure and mass effect are less pronounced in infancy in younger children because of compensatory and adaptive mechanism of surrounding brain structures. Metastatic presentation of PCNS-NB is reported only in couple of cases via cervical lymph nodes and cerebrospinal fluid [33]. Therefore in evaluation of PCNS-NB complete screening neuroimaging of whole cranio-spinal neuroaxis should be performed to rule out any metastatic spread through the CSF. In general, PCNS-NB appears like other solid CNS tumours in brain MRI. They can be purely solid or solid-cystic. Solid component of tumours are T1 and T2 hypointense with mild hyperintensity on DWI sequences and inhomogenous contrast enhancement and increased relative cerebral blood volume (rCBV) on perfusion images. Cystic component of tumour appears hyperintense due to hyperproteieic content. MRS sequences show increase in choline peak and inversion of choline/NAA ratio, but none of these imaging parameters are unique to the PCNS-NB. It is essential to understand that there are no tumour markers or radiological markers which can reliably differentiate PCNS-NB from other tumours. Two essential criteria for defining PCNS-NB is presence of classical histology and absence of systemic neuroblastoma.

The outcome of PCNS-NB depends on age, the tumour's aggressiveness, tumour subtype, locations, histology and extension. Surgery is the treatment of choice, and adjuvant radiotherapy improves survival. Safety and outcome of radiotherapy are not well established in infants and younger population but need to be viewed in light of improved survival obtained by adjuvant radiotherapy.

3. Summary and perspectives

3.1 Prognostic factors

Younger age group, a limited number of lesions, ganglioneuroblastoma subtype and surgical management, are found to be positive prognostic factors in PCNS-NB. Neuroblastoma has complex heterogeneous nature with varied prognosis, infants <1 year of age tend to have maximum overall survival with the tumour spontaneously regressing in some infants on the one hand and having widespread metastasis on the other hand [2, 12]. Studies have found best overall survival in infants <1 year of age and relatively less short term adverse events in age > 40 years with a 1-year survival of 57.2% [16].

3.2 Management options

In the population-based studies, patients with extensive disease, multiple lesions, and metastasis were more often offered conservative management as surgical excision was not feasible [16]. Surgical excision is often referred to as the first line of management in the treatment of PCNS-NB, whenever feasible [4]. Differentiation in ganglioneuroblastoma lies in between malignant neuroblastoma and benign ganglioneuroma. Ganglioneuroblastoma subtype is found to be associated with a good prognosis. Studies show that the ganglioneuroblastoma subtype rarely infiltrates and tends to be localised with less incidence of metastatic deposits [16, 34]. This explains that patients with this subtype are likely to be offered surgery and benefit from surgical excision with overall better survival. Ganglioneuroblastoma typically has a high invasive behaviour but slower multiplication rate and the asymptomatic period of up to 60 months has been reported after surgical excision [35, 36].

3.3 Adjuvant radiotherapy

Adjuvant radiotherapy of the primary site is the standard of care in high-risk neuroblastoma patients to reduce the risk of recurrence [6, 37]. Bennett et al. [7] suggested prophylactic irradiation craniospinal axis due to high propensity of CSF metastasis and recurrence of PCNS-NB [6]. However, the role of radiotherapy in PCNS-NB is not well elucidated. This is because the side effects of radiotherapy in the younger age group of radionecrosis and cognitive decline limit its applicability. Lu et al. [16] found a variable practice pattern of adjuvant radiotherapy and reported better survival and no significant side effects of radiotherapy, contrary to other studies.

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